Title

Prevention or reversal of weight gain associated with the use of antipsychotic or mood stabilizing drugs by means of the use of histamine H_2-receptor antagonists.

Technical Field

The present invention relates to improving treatment for patients with schizophrenia and other psychoses, bipolar disorders, depressive illness, impulse-control disorders, and related conditions.

Background of the Invention

In the last few years, tremendous advances have been made in the treatment of mental illness using newly-developed medications. Drugs such as olanzapine have made it possible for many patients with schizophrenia, manic depression, or other serious conditions to lead relatively normal lives. Unfortunately, many of these medicines cause weight gain, often in excess of forty pounds. Patients, in some cases, refuse to take a medication causing significant weight gain, no matter how effective it is for their illness. No method of preventing this weight gain has thus far been successful.

Accordingly, olanzapine, an atypical antipsychotic, is being increasingly used not only for schizophrenia but also in the treatment of bipolar disorder, obsessive compulsive disorder, pervasive developmental disorder, dementia, and other

illnesses. The most clinically significant limitation to the use of olanzapine appears to be the substantial weight gain (7 kilograms or more) in up to forty percent of patients. See, for example, Masand PS. Weight gain associated with atypical antipsychotics. J Psychotic Disorders. 1998; 2(3): 4-6. At present, there is no way to prevent or treat weight gain associated with the use of psychotropic active agents except through increased physical activity or decreased caloric intake.

The mechanisms for weight gain associated with anti-psychotics such as olanzapine, which has a broad receptor profile, are not known. See, for example, Bymaster FP, Rasmussen K, Calligaro DO et al., In vitro and in vivo biochemistry of olanzapine: A novel, atypical antipsychotic drug. J Clin Psychiatry. 1997; 58 (suppl 10): 28-36. Other predictors of antipsychotic-associated weight gain include increased appetite, clinical improvement, and underweight baseline Body Mass Index, although these findings are not specific to olanzapine. See Kinon BJ, Basson B, Szymanski K et al. Predictors of weight gain in olanzapine treatment. 38th Annual Meeting of the New Clinical Drug Evaluation Unit, June, 1998.

Accordingly, it is an object of the present invention to prevent or reduce weight gain in patients using antipsychotic and mood stabilizing medication.

Summary of the Invention

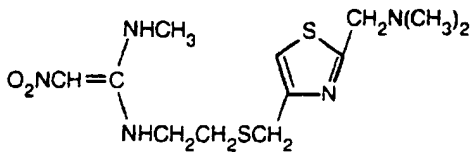
The present invention prevents and reverses weight gain associated with the use of olanzapine and other antipsychotic drugs. The combination of psychoactive drugs and histamine H_2-receptor antagonists may represent a combined single dose delivery system or multiple drug regimen taken at preselected times. The psychoactive drugs are dosed as recommended by the manufacturer and the histamine H_2-receptor antagonists are dosed as for use in maintenance treatment of duodenal ulcer.

Thus, the present invention relates to a method for the prevention or reversal of weight gain associated with the use of olanzapine or other antipsychotic drugs such as clozapine, risperidone, quetiapine or similar agents; or, with mood stabilizing drugs such as divalproex sodium, valproic acid, mirtazapine or similar anti-mania or antidepressant agents through the concomitant use of a safe and effective amount of a histamine H_2-receptor antagonist such as nizatidine, famotidine, cimetidine, ranitidine or similar agents.

Detailed Description of the Invention

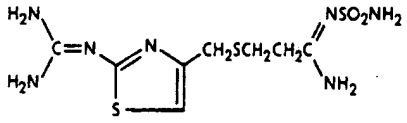
I. The Histamine H_2-Receptor Antagonists

Nizatidine [Axid (Lilly)] is a histamine H_2-receptor antagonist. Chemically, it is N -[2-[[[2-[(dimethylamino)methyl] -4- thiazolyl] methyl]thio]ethyl]-N'-methyl -2- nitro -1,1-ethenediamine. Its structural formula is:



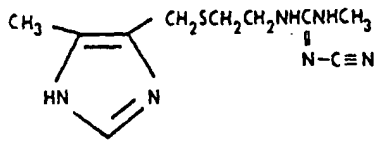
Nizatidine is a competitive, reversible inhibitor of histamine at the histamine H_2-receptors, particularly those in the gastric parietal cells and is an off-white to white crystalline solid that is soluble in water. The recommended oral dosage in adults with active duodenal ulcer, gastroesophageal reflux disease, or active benign gastric ulcer is 300 mg at bedtime. Maintenance of healed duodenal ulcer has a recommended oral dosage for adults of 150 mg once per day at bedtime. Dosages for use in patients with impaired renal function or other clinical conditions require appropriate adjustment to compensate for reduced metabolic clearance of the active agent. Currently this medication is available commercially in capsule form for oral administration as 150 mg or 300 mg of nizatidine, combined with gelatin, pregelatinized starch, dimethacone, starch, titanium dioxide, yellow iron oxide, and other inactive ingredients. In addition, the 150 mg capsule contains magnesium stearate and the 300 mg capsule contains croscarmellose sodium, povidone, red iron oxide, and talc.

Famotidine [Pepcid (Merck)] is a histamine H_2-receptor antagonist. Chemically, it is N'-(aminosulfonyl) -3- [[[2-[(diaminomethylene)amino] -4- thiazolyl] m-ethyl]thio] propanimidamide. Its structural formula is:



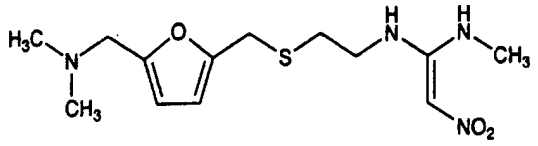
Famotidine is a competitive inhibitor of histamine H_2-receptors which has a primary clinically important pharmacologic activity of inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed, while changes in pepsin secretion are proportional to volume output. Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol. Currently this medication is available commercially in either 20 mg or 40 mg tablets or in oral solution. The recommended oral dosage for adults for active duodenal ulcer, active benign gastric ulcer, or gastroesophageal reflux disorder is 40 mg once a day at bedtime. Maintenance of healed duodenal ulcer has a recommended oral dosage for adults of 20 mg at bedtime. The tablet may contain either 20 mg or 40 mg of famotidine as well as inactive ingredients including hydroxypropyl cellulose, hydroxypropylmethyl cellulose, iron oxide, magnesium stearate, microcrystalline cellulose, cornstarch, talc, and titanium dioxide.

Cimetidine [Tagamet (SmithKline Beecham)] is a histamine H_2-receptor antagonist. Chemically, it is *N*''-cyano-*N*-methyl-*N*'-[2- [[(5-methyl-1 *H*-imidazol-4-yl) methyl] thio]-ethyl]-guanidine. Its structural formula is:



Cimetidine competitively inhibits the action of histamine at the histamine H_2-receptors of the parietal cells. It inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin. Cimetidine is soluble in alcohol, slightly soluble in water, very slightly soluble in chloroform, and insoluble in ether. Cimetidine hydrochloride is freely soluble in water, soluble in alcohol, very slightly soluble in chloroform, and practically insoluble in ether. This medication is currently available commercially as a tablet or liquid for oral administration and, as the hydrochloride, for intramuscular or intravenous injection. The recommended oral dosage for adults for active duodenal ulcer, active benign gastric ulcer, and gastroesophageal reflux disease is 800 mg once a day at bedtime. The maintenance dosage for healed duodenal ulcer is 400 mg once a day at bedtime. The tablet form contains 200 mg, 300 mg, 400 mg, or 800 mg of cimetidine and inactive ingredients consisting of cellulose, D&C Yellow No. 10, FD&C Blue No. 2, FD&C Red No. 40, FD&C Yellow No. 6, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, povidone, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, starch, titanium dioxide, and trace amounts of other inactive ingredients.

Ranitidine [Zantac (Glaxo Wellcome)] is a histamine H_2-receptor antagonist. Chemically, it is N[2-[[[5-[(dimethylamino)methyl]-2- furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1 -ethenediamine, hydrochloride. Its structural formula is:



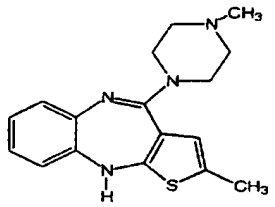
Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H_2- receptors, including receptors on the gastric cells. It inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, betazole, and pentagastrin. Ranitidine hydrochloride is a white to pale yellow, granular substance that is soluble in water. The medication is currently available commercially as a tablet, capsule, syrup, and injectable. The recommended oral dosage in adults for active duodenal ulcer, active benign gastric ulcer, gastroesophageal reflux disorder, and healing gastric ulcers is the equivalent of 150 mg of ranitidine twice a day. The recommended adult maintenance dosage for healing duodenal ulcers is 150 mg once a day at bedtime. The tablet form contains either 168 mg of ranitidine hydrochloride (equivalent to 150 mg of ranitidine) or 336 mg of ranitidine hydrochloride (equivalent to 300 mg of ranitidine) as well as inactive ingredients including FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin, and yellow iron oxide.

2. Th Psychotropic Activ Drugs

a. Anti-psychotic Drugs

The antipsychotic drugs of the instant invention are referred to as non-conventional or atypical antipsychotic drugs and are based upon olanzapine and related pharmaceutical compounds. They are to be contrasted with conventional or typical antipsychotic drugs which are based upon thorazine and its derivatives.

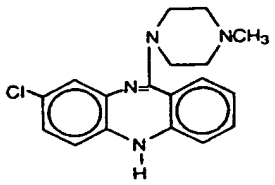
Olanzapine [Zyprexa (Lilly)] is an antipsychotic agent belonging to the thienobenzodiazepine class. The chemical designation is 2-methyl -4- (4-methyl-1-piperazinyl)-10*H*-thieno [2,3-*b*] [1,5]benzodiazepine. Its structural formula is:



Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$, dopamine D_{1-4}, muscarinic M_{1-5}, histamine H_1, and adrenergic alpha $_1$ receptors. It binds weakly to $GABA_A$, BZD and beta-adrenergic receptors. The mechanism of action is unknown. Olanzapine is a yellow crystalline solid, which is practically insoluble in water. The recommended target dose is 10 mg per day administered on a once-a-day schedule without regard to meals. The initial dosage is 5 to 10 mg with subsequent dosage adjustments

being made as indicated to achieve maximum effectiveness. The medication is currently available commercially in tablet form containing 2.5 mg, 5 mg, 7.5 mg, or 10 mg of olanzapine. Inactive ingredients include carnauba wax, color mixture white, crospovidone, FD&C Blue No. 2 Aluminum Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients.

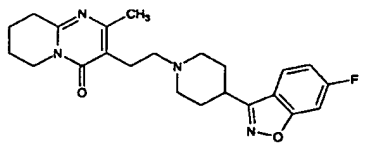
Clozapine [Clozaril (Novartis Pharm.)] is an antipsychotic drug which is a tricyclic dibenzodiazepine derivative. Chemically, it is 8-chloro -11- (4-methyl-1-piperazinyl)-5*H*-dibenzo [*b,e*][1,4] diazepine. Its structural formula is:



Clozapine is classified as an "atypical" antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine mediated behaviors differ from those exhibited by more typical antipsychotic drug products. In particular, although clozapine does interfere with the binding of dopamine at D_1, D_2, D_3,and D_5 receptors, and has a high affinity for the D_4 receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy. It also acts as an antagonist at adrenergic, cholinergic, histaminergic, and serotonergic receptors.

Clozapine is a yellow, crystalline powder, very slightly soluble in water. The recommended adult target dose is 300 mg to 450 mg per day titrated to maximum effectiveness but not to exceed 900 mg per day. The medication is commercially supplied in 25 mg and 100 mg tablets of clozapine which also contain inactive ingredients including colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch, and talc.

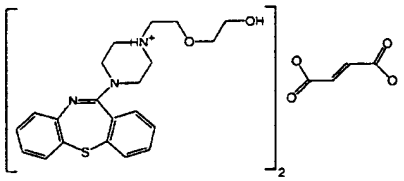
Risperidone [Risperdal (Janssen)] is an antipsychotic agent which is a benzisoxazole derivative. Chemically, it is 3- [2-[4-(6-fluoro- 1,2-benzisoxazol-3 -yl) - 1- piperidinyl] ethyl]-6,7, 8,9-tetrahydro-2-methyl-4*H*-pyrido [1,2-a] pyrimidin-4-one. Its structural formula is:



Risperidone is a selective monoaminergic antagonist with high affinity for the serotonin type 2 (5 HT_2), dopamine type 2 (D_2), alpha $_1$ and alpha $_2$ adrenergic, and H_1 histaminergic receptors. Risperidone antagonizes other receptors but with lower potency. It has low to moderate affinity for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, a weak affinity for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity for cholinergic, muscarinic or beta $_1$ and beta $_2$ adrenergic receptors. The mechanism of action of risperidone is unknown. Risperidone is a white to

slightly beige powder which is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 *N* HCl. The recommended adult target dose is in the range of 4 mg to 6 mg per day, given in divided doses. Antipsychotic efficacy was demonstrated in a dose range of 4 mg to 16 mg per day in clinical trials, however. Risperidone is commercially available in tablets containing 1 mg, 2 mg, 3 mg, or 4 mg of the active ingredient. It is also available in oral solution. Inactive ingredients in the tablet form include: colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets may also contained talc, titanium dioxide, FD&C Yellow No. 6 Aluminum Lake, D&C Yellow No. 10, and FD&C Blue No. 2 Aluminum Lake.

Quetiapine fumarate [Seroquel (Zeneca)] is an antipsychotic drug which is a dibenzothiazepine derivative. Chemically, it is 2-[2-(4-dibenzo [*b,f*] [1,4]thiazepin-11-yl- I -piperazinyl) ethoxy]ethanol fumarate (2:1)(salt). Its structural formula is:

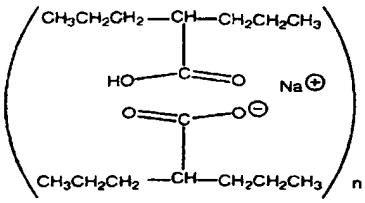


Quetiapine fumarate is an antagonist at multiple neurotransmitter receptors in the brain including serotonin $5HT_{1a}$ and $5HT_2$, dopamine D_1 and D_2, histamine H_1, and

adrenergic alpha $_1$ and alpha $_2$ receptors. It has no appreciable affinity at cholinergic, muscarinic, or benzodiazepine receptors. The mechanism of action of quetiapine is unknown. Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water. The recommended adult target dose is 300 mg to 400 mg daily, given in divided doses. Antipsychotic efficacy was demonstrated in a dose range of 150 mg to 750 mg per day in clinical trials. Quetiapine is commercially available in tablet form containing 25 mg, 100 mg, and 200 mg of the active ingredient in the form of the fumarate salt. Inactive ingredients include povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide. The 25 mg tablet contains red ferric oxide and yellow ferric oxide while the 100 mg tablet contains only yellow ferric oxide.

b. Mood Altering Drugs

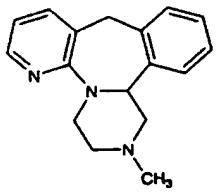
Divalproex [Depakote (Abbott)] is an anti-epileptic and anti-mania drug which is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. As used herein, "divalproex" and "valproate" are intended to include valproic acid and their pharmaceutically-acceptable salts. Chemically, it is sodium hydrogen bis(2-propylpentanoate). Its structural formula is:



Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanism by which valproate exerts its therapeutic effect have not been established however it has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA). Divalproex sodium occurs as a white powder. The recommended initial adult dosage is 750 mg daily in divided doses with a maximum recommended dosage of no greater than 60 mg/kg/day. Divalproex sodium is available in tablet form for oral administration in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg, or 500 mg of valproic acid. Inactive ingredients include cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, and vanillin. Individual tablets may contain colorants including FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, iron oxide, FD&C Red No. 30, and FD&C Blue No. 2.

Mirtazapine [Remeron (Organon)] is an antidepressant drug which belongs to the piperazino-azepine group of compounds. Chemically, it is 1,2,3,4,10,14b-

hexahydro-2-methylpyrazino [2,l-a]pyrido [2,3-c]benzazepine. Its structural formula is:



Mirtazapine is an antidepressant with potent antagonism of $5HT_2$ and $5HT_3$ receptors but no significant affinity for $5HT_{1A}$ and $5HT_{1B}$ receptors. It is also a potent antagonist of histamine H_1. It is a moderate peripheral alpha $_1$ adrenergic antagonist and a moderate antagonist at muscarinic receptors. The mechanism of action is unknown although it is suggested that mirtazapine enhances central noradrenergic and serotonergic activity. Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water. The recommended starting dose for mirtazapine is 15 mg per day, administered in a single dose, preferably in the evening prior to sleep. The effective dose range is generally 15 mg to 45 mg per day. Mirtazapine is available commercially in tablets containing 15 mg or 30 mg of the active agent. Inactive ingredients include cornstarch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose, and other inactive ingredients.

3. Use of Drugs in the Instant Invention

Generally, the antipsychotic drug is selected from olanzapine, clozapine, risperidone and quetiapine. The antipsychotic drug is typically in a concentration of 10% to 90%, 30% to 60% and 50% weight of the combined drugs.

Generally, the mood stabilizing drug is selected from divalproex sodium, valproic acid and mirtazapine. The mood stabilizing drug is typically in a concentration of 10% to 90%, 30% to 60% and 50% weight percent of the combined drugs.

The dosage forms used in the present invention optionally may be formulated for controlled release, sustained release, or orally disintegrating forms.

In practicing the method of treatment of the present invention, the histamine H_2-receptor is administered to a patient taking olanzapine or another of the psychotropic active agents as described above. The psychotropic active agent will be administered using conventional routes of delivery and at conventional dosage levels, consistent with good practices as described in the PDR which as to each drug is incorporated herein by reference. The histamine H_2-receptor antagonist may be administered to the patient in any way known in the art, although oral administration will generally be the most convenient. The histamine H_2-receptor antagonist is administered in an amount that is safe and effective for minimizing the

weight gain associated with psychotropic therapy, initially at the level recommended for the maintenance treatment of duodenal ulcer disease.

The dosages of the drug combinations are empirically derived and are based on typical clinical usage of the non-combined forms. The psychoactive drugs are dosed as recommended by the manufacturer and to the level of maximal benefit for the patient. The histamine H_2-receptor antagonists are dosed as for use in the maintenance treatment of duodenal ulcer. The actual composition of the combination may vary as more clinical experience is gained.

The present invention also encompasses a combination drug that includes both the histamine H_2-receptor antagonist and the psychotropic active agent as described above. The combination of drugs is typically formulated as a tablet or capsule for oral administration, although other routes of administration, such as intravenous injection can also be used. A tablet or capsule for oral administration of the present invention would typically include, in a pharmaceutically- acceptable form:

Olanzapine from about 1mg to10mg or greater combined with nizatidine 150 mg or ranitidine 150 mg or famotidine 20 mg or cimetidine 400 mg;

Risperidone from about 0.5 mg to 8 mg or greater combined with nizatidine 150 mg or ranitidine 150 mg or famotidine 20 mg or cimetidine 400 mg;

Quetiapine from about 25 mg to 800 mg or greater combined with nizatidine 150 mg or ranitidine 150 mg or famotidine 20 mg or cimetidine 400 mg;

Clozapine from about 25 mg to 900 mg or greater combined with nizatidine 150 mg or ranitidine 150 mg or famotidine 20 mg or cimetidine 400 mg;

Mirtazapine from about 7.5 mg to 45 mg or greater combined with nizatidine 150 mg or ranitidine 150 mg or famotidine 20 mg or cimetidine 400 mg;

Divalproex sodium from about 125 mg to 3000 mg or greater combined with nizatidine 150 mg or ranitidine 150 mg or famotidine 20 mg or cimetidine 400 mg.

Conventional formulational aids, such as fillers, coatings, preservatives, disintegration aids, colorings and flavorings, can also be included at their conventional art-established levels.

By "safe and effective", as used herein, is meant that the compounds and other ingredients used in present methods and compositions, are suitable for use in

contact with the tissues of humans without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable risk/benefit ratio and are able, in a significant number of normal patients, to produce to some measurable extent the desired result.